# Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials

Non-small Cell Lung Cancer Collaborative Group


## Abstract

***Objective*—To evaluate the effect of cytotoxic chemotherapy on survival in patients with non-small cell lung cancer.**

***Design*—Meta-analysis using updated data on individual patients from all available randomised trials, both published and unpublished.**

***Subjects*—9387 patients (7151 deaths) from 52 randomised clinical trials.**

***Main outcome measure*—Survival.**

***Results*—The results for modern regimens containing cisplatin favoured chemotherapy in all comparisons and reached conventional levels of significance when used with radical radiotherapy and with supportive care. Trials comparing surgery with surgery plus chemotherapy gave a hazard ratio of 0·87 (13% reduction in the risk of death, equivalent to an absolute benefit of 5% at five years). Trials comparing radical radiotherapy with radical radiotherapy plus chemotherapy gave a hazard ratio of 0·87 (13% reduction in the risk of death; absolute benefit of 4% at two years), and trials comparing supportive care with supportive care plus chemotherapy 0·73 (27% reduction in the risk of death; 10% improvement in survival at one year). The essential drugs needed to achieve these effects were not identified. No difference in the size of effect was seen in any subgroup of patients. In all but the radical radiotherapy setting, older trials using long term alkylating agents tended to show a detrimental effect of chemotherapy. This effect reached conventional significance in the adjuvant surgical comparison.**

***Conclusion*—At the outset of this meta-analysis there was considerable pessimism about the role of chemotherapy in non-small cell lung cancer. These results offer hope of progress and suggest that chemotherapy may have a role in treating this disease.**


**Non-small Cell Lung Cancer Collaborative Group**
The collaborative group members and the organisations and groups that collaborated in the meta-analysis are listed at the end of the article.

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## Introduction

Worldwide more than half a million new cases of lung cancer are diagnosed annually.[1] About 80% of these tumours are of non-small cell histological type,[2] including adenocarcinomas and squamous cell and large cell carcinomas. Non-small cell lung cancer is a leading cause of deaths related to cancer,[3] and five year survival across all stages is about 12%.[4] Surgery is the treatment of choice, but only about 20% of tumours are suitable for potentially curative resection.[5] A further, small proportion of patients, usually presenting with locally advanced disease, undergo radical thoracic radiotherapy. Most patients with late stage or metastatic disease are treated palliatively.

Although cytotoxic chemotherapy is used routinely in treating small cell lung cancer, its role in non-small cell lung cancer remains controversial. A recent international consensus report concluded that postoperative chemotherapy was of unproved benefit and should be considered experimental.[6] This uncertainty remains despite over 30 years of research involving around 10 000 patients in over 50 randomised clinical trials examining the efficacy of chemotherapy when combined with local treatment or best supportive care. With few exceptions, however, most of these trials were too small to reliably detect moderate treatment effects. Only four trials involved more than 400 patients and about half the trials each recruited fewer than 100 patients. Consequently, although a few trials have reported significant results, both for and against chemotherapy, most trials have been inconclusive and the pattern of results could be consistent with moderate treatment benefits. The most reliable and unbiased way to assess the evidence and to establish the size of any possible treatment effect is to conduct a meta-analysis of updated data on individual patients.[7]

Such a meta-analysis was therefore initiated by the British Medical Research Council's Cancer Trials Office, Cambridge; the Institut Gustave Roussy, Villejuif, France; and the Istituto Mario Negri, Milan, Italy, and was carried out on behalf of the Non-small Cell Lung Cancer Collaborative Group.

Patients with non-small cell lung cancer can be classified into three broad categories according to the primary treatment that they receive: surgery, radical, or potentially curative radiotherapy and supportive care. There is a continuum of patients both within and between these categories, but we took the pragmatic approach of asking general questions about whether chemotherapy is effective in each of these groups. We made comparisons corresponding to the type of treatment usually considered at the time of presentation: early disease (surgery *v* surgery plus chemotherapy; surgery plus radiotherapy *v* surgery plus radiotherapy plus chemotherapy); locally advanced disease (radical radiotherapy *v* radical radiotherapy plus chemotherapy); and advanced disease (supportive care *v* supportive care plus chemotherapy). The main objective was to investigate the effect of chemotherapy on survival in these four treatment settings. A further objective was to assess whether any possible effects were consistent in well defined subgroups of patients.

## Methods

The methods and investigations were prespecified in clinical and analysis protocols. (Copies of these documents are available on request.) Collection and validation of data were carried out in two centres (Cancer Trials Office and the Institut Gustave Roussy), and after the data had been cross checked, a common database was agreed.

### ELIGIBILITY CRITERIA

Trials were eligible for inclusion if they randomised

patients with non-small cell lung cancer between one of the four primary treatments and the same treatment plus an established form of cytotoxic chemotherapy. Each trial had to be unconfounded and be believed to have been randomised in a way that precluded prior knowledge of the next treatment to be assigned. Trials were eligible if they started recruitment after 1 January 1965 and completed recruitment by 31 December 1991. Trials allowing patients to have received chemotherapy before randomisation were ineligible. Trials with surgery and radical radiotherapy should not have permitted previous treatment for any other malignancy in the surgical comparison. Trials were eligible only if they had randomised patients who had undergone a potentially curative resection. Trials of neo-adjuvant treatment were not included in this comparison as it was considered too early to evaluate such trials. Trials of radical radiotherapy using orthovoltage radiotherapy or a total radiation dose of $<30$ Gy were excluded, as were trials in which drugs were used with the primary aim of sensitisation to radiation.

### IDENTIFICATION OF TRIALS

To avoid publication bias both published and unpublished studies were included, and several methods were used to identify all relevant trials. Computerised bibliographic searches with Medline and CancerCD were supplemented with hand searches of meetings abstracts, bibliographies of books, reviews, and specialist journals. Trial registers managed by the National Cancer Institute (PDQ, ClinProt), United Kingdom Coordinating Committee for Cancer Research, and the Union Internationale Contre le Cancer were also consulted. Experts, pharmaceutical companies, and all trialists who took part in the meta-analysis were also asked to help to identify trials.

### DATA

Updated information on survival status and date of last follow up was sought, together with treatment allocated, date of randomisation, age, sex, histological cell type, stage, and performance status. To avoid potential bias this information was also required for patients who had been excluded from the investigators' analysis. All data were checked for internal consistency and against the trial protocol and published reports. Range checks were performed and extreme values were checked with the trialists. Each trial was analysed individually, and the resulting survival analyses and trial data were sent to the trialists for verification.

### ANALYSIS

The protocol specified that trials would be subdivided according to the use of cisplatin, primarily as an objective means of specifying modern and older chemotherapy regimens. Classification based on date was considered unsatisfactory as it has less clinical meaning and trials take different periods of time to complete. There was also much interest in the role of cisplatin. Before the data were analysed, it became clear that trials in the groups not using cisplatin were either early trials that used alkylating agents (often administered orally) over a prolonged period of time or recent trials using modern regimens not containing cisplatin. Trials were therefore finally classified into the following categories: (*a*) regimens containing cisplatin, (*b*) regimens using alkylating agents for more than one year, (*c*) regimens containing etoposide or vinca alkaloids but not cisplatin, and (*d*) other regimens. Each trial could belong to only one category.

All analyses were carried out on intention to treat—that is, patients were analysed according to their allocated treatment—irrespective of whether they received that treatment.

### STATISTICS

For each comparison, survival analyses were stratified by trial, and the log rank expected and observed numbers of deaths were used to calculate individual and overall pooled hazard ratios with the fixed effect model.[8] Thus the time to death for individual patients was used within trials to generate the hazard ratio representing the overall risk of dying receiving treatment compared with the control. To investigate the effect of chemotherapy within prespecified subgroups, similar stratified analyses were performed. A hazard ratio was calculated for each prespecified category—for example, for males and for females within each individual trial—and these ratios were then combined to give overall hazard ratios for males and females for each treatment setting.

As the absolute difference in treatment effect depends on the hazard ratio and the underlying baseline survival—and the way that these interrelate is not intuitive—the results are presented as both hazard ratios and absolute differences. Here, as in the other analyses, proportional hazards are assumed. The absolute survival difference was calculated by using survival on the control arms of cisplatin based trials within each treatment comparison as a baseline at given points in time as follows:

Absolute benefit = (exponential (hazard ratio $\times$ ln baseline survival)) − baseline survival

$\chi^2$ Heterogeneity tests[10] were used to test for gross statistical heterogeneity over all trials in a comparison ($\chi^2_{HetT}$), between chemotherapy categories (test for interaction $\chi^2_{HetB}$) and within chemotherapy categories ($\chi^2_{HetW}$), ($\chi^2_{HetT}=\chi^2_{HetB}+\chi^2_{HetW}$). When appropriate, the heterogeneity within a single category ($\chi^2_{HetC}$) has also been calculated. These tests are aimed primarily at detecting quantitative differences—that is, differences in size rather than direction—and were chosen because qualitative differences were not anticipated. Whenever gross statistical heterogeneity was detected the rationale for combining trials was questioned and the source of heterogeneity investigated, rather than using a random effects model.[11]

Survival curves are presented as simple (non-stratified) Kaplan-Meier curves.[12] All P values quoted are two sided. Unless otherwise specified $\chi^2$ values are on one degree of freedom.

## Results

In all, 91 trials were identified as potentially eligible for the meta-analysis. Thirty three of these were found to be ineligible and therefore excluded (appendix 1). Of the 58 eligible trials[13-62] (Lung Cancer Study Group protocol 853, unpublished data; M Imaizumi, personal communication; Finnish Lung Cancer Study Group, unpublished data; European Organisation for Research and Treatment of Cancer protocol 08861, unpublished data; G Anderson, personal communication; European Organisation for Research and Treatment of Cancer protocol 08842, unpublished data; South Western Oncology Group protocol 8300, unpublished data), data were not available from six as they had been lost or destroyed or were untraceable[25 26 49-52] (appendix 1). Data from 52 randomised trials and 9387 patients were therefore included in this meta-analysis.

### EARLY DISEASE

*Surgery v surgery plus chemotherapy*

Data were available from 14 trials (4357 patients and 2574 deaths) (table I). Five trials used long term alkylating agents (2145 patients, 1670 deaths), mainly cyclophosphamide and nitrosourea; eight more recent trials (1394 patients, 614 deaths) used cisplatin based combination chemotherapy, three used the regimen of

cisplatin, doxorubicin, and cyclophosphamide (CAP), and three used cisplatin with vindesine. The intended dose of cisplatin ranged from 40 mg/m² to 80 mg/m² per cycle and total dose from 50 mg/m² to 240 mg/m². A further three trials used other drug regimens, all of which included tegafur or UFT (tegafur plus uracil), a drug similar to fluorouracil.[63] In all the trials chemotherapy was scheduled to start no later than six weeks after surgery.

The results showed considerable diversity and evidence of a difference in direction of effect between the predefined categories of chemotherapy (table II, fig 1). The test for overall statistical heterogeneity was conventionally significant (P=0·02), as was the test for interaction (P=0·004). No evidence existed, however, of heterogeneity within each category (P=0·21). Thus it is more useful to concentrate on the results for each of the predefined chemotherapy categories than on the overall result.

The results for long term alkylating agents were consistent—the hazard ratio estimates all favoured surgery alone with a combined hazard ratio of 1·15 (P=0·005). This 15% increase in the risk of death translates to an absolute detriment of chemotherapy of 4% at two years and 5% at five years. For regimens containing cisplatin (figures 1 and 2) the pattern of results was again consistent, with hazard ratio estimates for most trials favouring chemotherapy. No obvious statistical heterogeneity existed in the results of these trials ($\chi^2_{HetC}$=5·92, df=7, P=0·55), and the overall hazard ratio of 0·87 (P=0·08), or 13% reduction in the risk of death, suggested an absolute benefit from chemotherapy of 3% at two years and 5% at five years (table II), although on their own these results were not conclusive. The 95% confidence intervals for absolute difference in survival were consistent with a 0·5% detriment to a 7% benefit of chemotherapy at two years and similarly consistent with a 1% detriment to a 10% benefit at five years.The trials that were classified as using other regimens gave an estimated hazard ratio of 0·89 in favour of chemotherapy (P=0·30), but there was insufficient information to draw any reliable conclusions.

TABLE I—*Trials comparing surgery with surgery plus chemotherapy. Drugs were given intravenously and doses per cycle were in mg/m² unless stated otherwise*

| Trial | Period of recruitment | Drugs used | Drug dose/ chemotherapy cycle | Cycles |
|---|---|---|---|---|
| MRC LU02 (Girling *et al*[53]) | 1965-8 | (i) Cyclophosphamide* | 200/75† | Daily treatment 2 years |
| | | (ii) Busulphan* | 4/1·5 | |
| VASAG (Shields *et al*[54]) | 1968-73 | (i) Cyclophosphamide | 40‡ | 15 |
| | | (ii) Cyclophosphamide | 40‡ | |
| | | Methotrexate | 50§ | |
| EORTC 08741a (Israel *et al*[55]) | 1973-9 | Lomustine* | 70 | 13 |
| | | Cyclophosphamide | 1000 | |
| | | Methotrexate | 40 | |
| VASOG 5 (Shields *et al*[56]) | 1973-9 | Lomustine* | 70 | 9 |
| | | Nitrogen mustard* | 2000 | 52 |
| WPL 7351 (Mountain *et al*[57]) | 1974-6 | Lomustine* | 130 | 17 |
| OLCSG 1a (Sawamura *et al*[58]) | 1982-7 | Tegafur* | 600-800§ | Daily treatment > 1 year |
| OLCSG 1b (Sawamura *et al*[58]) | 1982-6 | Doxorubicin | 100§ | 3 |
| | | Mitomycin C | 20§ | |
| | | Tegafur* | 600-800§ | Daily treatment |
| | | followed by | | |
| | | Tegafur* | 600-800§ | Daily treament > 1 year |
| SGACLA 1 (SGACLC[59]) | 1982-5 | Mitomycin C | 0·08‡ | 10 |
| | | Cyclophosphamide | 2‡ | |
| | | Tegafur* | 12‡ | Daily treatment > 6 months |
| WJSG 2 (Teramatsu[20]) | 1985-8 | (i) Cisplatin | 50 | 1 |
| | | Vindesine/ | 6–9§ | |
| | | UFT* | 400§ | Daily treatment 1 year |
| | | (ii) UFT* | 400§ | Daily treatment 1 year |
| LCSG 801 (Feld *et al*[21]) | 1980-6 | Cisplatin | 60 | 4 |
| | | Doxorubicin | 40 | |
| | | Cyclophosphamide | 400 | |
| OLCSG 1c (Sawamura *et al*[58]) | 1982-7 | Cisplatin | 80 | 1 |
| | | followed by | | |
| | | Tegafur* | 600-800§ | Daily treatment > 1 year |
| FLCSG 1 (Niiranen *et al*[22]) | 1982-7 | Cisplatin | 40 | 6 |
| | | Doxorubicin | 40 | |
| | | Cyclophosphamide | 400 | |
| SGACLC 2 (unpublished) | 1985-7 | Cisplatin | 66 | 1 |
| | | Doxorubicin | 26 | |
| | | UFT* | 8‡ | Daily treatment > 6 months |
| IPCR, Chiba (Kimura *et al*[23]) | 1985-91 | Cisplatin | 80 | > 2 |
| | | Vindesine | 3 | |
| | | Mitomycin C‖ | 8 | |
| LCSG 853 (unpublished) | 1985-9 | Cisplatin | 60 | 4 |
| | | Doxorubicin | 40 | |
| | | Cyclophosphamide | 400 | |
| JLCSSG (Ohta *et al*[24]) | 1986-8 | Cisplatin | 80 | 2–3 |
| | | Vindesine | 6 | |

See appendix 2 for full names of trial groups. Roman numerals indicate multiple treatment arms.
*Given orally.
†After 10 days patients switched to maintenance chemotherapy. For first year only, drug doses were cyclophosphamide 150 mg and busulphan 3 mg.
‡Dose in mg/kg.
§Total dose.
‖Mitomycin C was added to regimen from 1990.

### *Surgery plus radiotherapy v surgery plus radiotherapy plus chemotherapy*

Data were available from all seven eligible trials (807 patients and 619 deaths), six of which used a cisplatin based regimen, with intended doses of cisplatin ranging from 40 mg/m² to 100 mg/m² per cycle and total dose from 80 mg/m² to 400 mg/m² (table III). Total planned doses of radiotherapy ranged from 40 Gy in 10 fractions to 65 Gy in 33 fractions, and the delay between surgery and the first adjuvant treatment was scheduled to be no longer than seven weeks.

The overall hazard ratio of 0·98 (P=0·76) was marginally in favour of chemotherapy (table II, fig 3). No gross statistical heterogeneity existed between the trials (P=0·73). For the cisplatin based trials (figures 3 and 4) the hazard ratio of 0·94 (P=0·46), or 6% reduction in the risk of death, favoured chemotherapy, suggesting a 2% absolute benefit at both two and five years. 95% Confidence intervals ranged from a 4% detriment to an 8% benefit at two years and from a 3% detriment to an 8% benefit at five years.

## LOCALLY ADVANCED DISEASE

### *Radical radiotherapy v radical radiotherapy plus chemotherapy*

Data were available from 22 trials (3033 patients and 2814 deaths) (table IV). Five trials used long term

TABLE II—*Main results of meta-analysis of chemotherapy in non-small cell lung cancer*

| | Control Arm Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Surgery | | | | Surgery plus radiotherapy | | | | Radical radiotherapy | | | | Supportive care | | | |
| | | | % Absolute benefit (baseline) | | | | % Absolute benefit (baseline) | | | | % Absolute benefit (baseline) | | | | % Absolute benefit (baseline) | |
| Drugs used | Hazard ratio (95% confidence interval) | P value | At 2 years (70%) | At 5 years (50%) | Hazard ratio (95% confidence interval) | P value | At 2 years (50%) | At 5 years (15%) | Hazard ratio (95% confidence interval) | P value | At 2 years (15%) | At 5 years (5%) | Hazard ratio (95% confidence interval) | P value | At 1 year (15%) | Median (4 months) |
| Long term alkylating agents | 1·15 (1·04 to 1·27) | 0·005 | −4 | −5 | 1·35 (0·83 to 2·20) | 0·23 | −11 | −7 | 0·98 (0·83 to 1·16) | 0·81 | 0·5 | 0·5 | 1·26 (0·96 to 1·66) | 0·095 | −6 | −1 month |
| Vinca alkaloid or etoposide | NA | NA | NA | NA | NA | NA | NA | NA | 0·87 (0·70 to 1·09) | 0·23 | 4 | 2 | 0·87 (0·64 to 1·20) | 0·40 | 4 | ½ month |
| "Other" drugs | 0·89 (0·72 to 1·11) | 0·30 | 3 | 4 | NA | NA | NA | NA | 0·98 (0·74 to 1·29) | 0·88 | 0·5 | 0·5 | NA | NA | NA | NA |
| Cisplatin based drugs | 0·87 (0·74 to 1·02) | 0·08 | 3 | 5 | 0·94 (0·79 to 1·11) | 0·46 | 2 | 2 | 0·87 (0·79 to 0·96) | 0·005 | 4 | 2 | 0·73 (0·63 to 0·85) | <0·0001 | 10 | 1½ months |

NA=not applicable.

| Trial | No of events/ No of patients entered: Surgery plus chemotherapy | Surgery | Observed − expected deaths | Variance |
|---|---|---|---|---|
| Long term alkylating agents: | | | | |
| MRC LUO2 | 415/428 | 209/215 | 18.22 | 143.32 |
| VASAG | 251/291 | 128/152 | 4,50 | 86.00 |
| EORTC 08741 | 38/71 | 36/75 | 5.82 | 18.06 |
| VASOG 5 | 292/424 | 261/417 | 20.63 | 137.53 |
| WPL 7351 | 25/36 | 15/36 | 6.36 | 9.83 |
| Subtotal | 1021/1250 | 649/895 | 55.53 | 394.74 |
| Other drugs: | | | | |
| OLCSG Ia | 30/163 | 28/158 | -0.09 | 14.47 |
| OLCSG Ib | 27/41 | 21/42 | 6.59 | 11.36 |
| SGACLC ACTLC I | 70/154 | 75/152 | -6.10 | 36.12 |
| WJSG 2 (2 and 3) | 38/108 | 49/100 | -9.79 | 21.49 |
| Subtotal | 165/466 | 173/452 | -9.39 | 83.44 |
| Cisplatin based: | | | | |
| LCSG 801 | 66/140 | 71/143 | -1.81 | 34.21 |
| OLCSG Ic | 5/12 | 7/16 | -0.19 | 2.93 |
| FLCSG I | 20/54 | 30/56 | -7.79 | 12.21 |
| SGACLC ACTLC2 | 64/165 | 68/167 | -4.80 | 32.88 |
| IPCR Chiba | 11/15 | 7/14 | 1.33 | 4.07 |
| WJSG 2 (I and 3) | 44/115 | 49/100 | -7.66 | 22.94 |
| LCSG 853 | 29/94 | 32/94 | -1.65 | 15.22 |
| JLCSSG | 59/111 | 52/98 | 0.98 | 27.38 |
| Subtotal | 298/706 | 316/688 | -21.58 | 151.83 |
| Total | 1484/2422 | 1138/2035 | 24.57 | 630.01 |

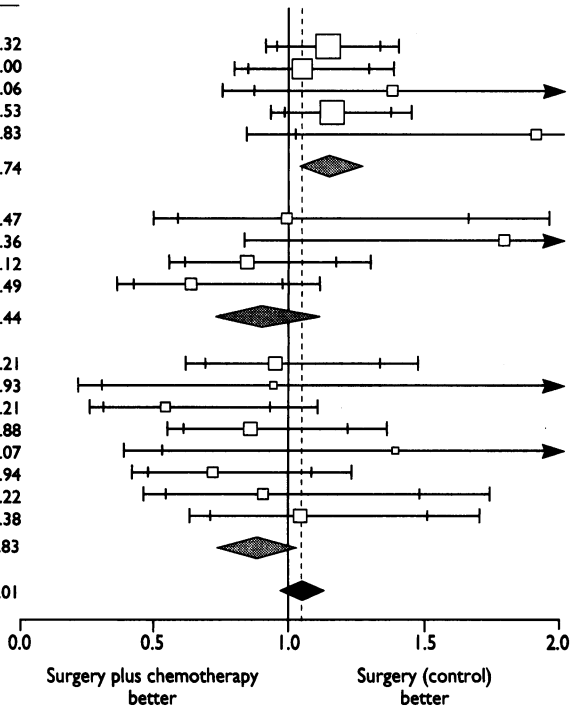


FIG 1—*Results of trials of surgery versus surgery plus chemotherapy (test for heterogeneity $\chi^2_{HetT}$=28·98, df=16, P=0·02; test for interaction $\chi^2_{HetB}$=10·97, df=2, P=0·004, $\chi^2_{HetW}$=18·01, df=14, P=0·21) (see tables for references to trials). As West Japan Study Group for Lung Cancer Surgery's second trial (WJSG 2) fell into two categories, patients in the control arm are included in subtotals of "other drugs" and "cisplatin based" but used only once in overall total, to calculate hazard ratio and confidence interval. The test for heterogeneity ($\chi^2_{HetT}$) was calculated by counting the study group's second trial as two separate trials. Each individual trial is represented by a square, the centre of which denotes the hazard ratio for that trial, with horizontal bars whose extremities denote the 99% confidence interval and inner bars mark the 95% confidence interval. The size of the square is directly proportional to the amount of information in the trial. The black diamond at the foot of the plot gives the overall hazard ratio when the results of all trials are combined, the centre of which denotes the hazard ratio and the extremities the 95% confidence interval (shaded diamonds represent the hazard ratio for the various specified categories of chemotherapy). Trials are ordered chronologically by date of start of trial (oldest first) within chemotherapy categories*

alkylating agents, mainly cyclophosphamide or nitrosourea in combination with methotrexate. Three used vinca alkaloids or etoposide, and three used "other" regimens, which in this comparison were mostly based on doxorubicin. Eleven trials (1780 patients, 1696 deaths) used chemotherapy regimens containing cisplatin, of which two used the regimen of cisplatin, doxorubicin, and cyclophosphamide and seven used a combination of cisplatin plus a vinca alkaloid or etoposide. Intended doses of cisplatin ranged from 40 mg/m² to 120 mg/m² per cycle and total doses from 120 mg/m² to 800 mg/m.[2] The intended radiation dose for cisplatin based trials ranged from 50 Gy in 20 fractions to 65 Gy in 30 fractions. Ten of these trials started chemotherapy before radiotherapy.

The results showed a significant overall benefit of chemotherapy (table II, fig 5). The hazard ratio of 0·90 (P=0·006), or 10% reduction in the risk of death, corresponded to absolute benefits of 3% at two years and 2% at five years. No gross statistical heterogeneity existed between trials (P=0·56), nor such strong evidence of a difference between chemotherapy categories, which was reflected in the non-significant test for interaction (P=0·59). Trials using long term alkylating agents and "other" regimens yielded a hazard ratio of 0·98 (P=0·81 and P=0·88 respectively), both marginally in favour of chemotherapy but inconclusive. Trials using regimens containing vinca alkaloids or etoposide also favoured chemotherapy, with a hazard ratio of 0·87 (P=0·23), a 13% reduction in the risk of death, but no firm conclusions can be drawn. Trials using cisplatin based chemotherapy provided the most information (more than 50%) and the strongest evidence for an effect in favour of chemotherapy (figures 5 and 6). The hazard ratio of 0·87 (P=0·005), or 13% reduction in the risk of death, was equivalent to absolute benefits of 4% (95% confidence interval 1% to 7%) at two years and 2% (1% to 4%) at five years. However, no firm evidence exists that the results of the trials using regimens containing vinca alkaloids or etoposide or of those using other regimens of modern drugs were any different from those using cisplatin based chemotherapy.

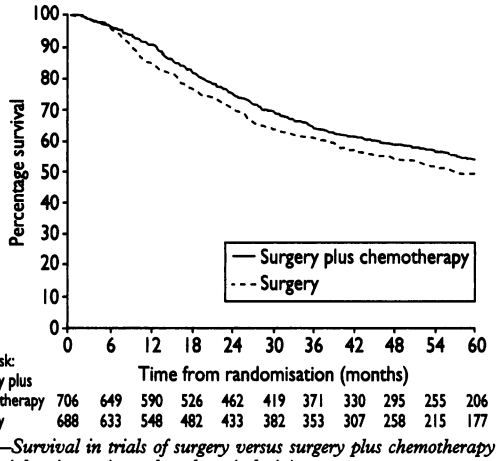


FIG 2—*Survival in trials of surgery versus surgery plus chemotherapy (only trials using regimens based on cisplatin)*

ADVANCED DISEASE

*Supportive care v supportive care plus chemotherapy*

Data were available from 11 trials (1190 patients and 1144 deaths) (table V). Two trials used long term alkylating agents and one used etoposide as a single agent. The remaining eight trials (778 patients, 761 deaths) used cisplatin based chemotherapy, seven of

TABLE III—*Trials comparing surgery plus radiotherapy with surgery plus radiotherapy plus chemotherapy. Drugs were given intravenously and doses per cycle were in mg/m² unless stated otherwise*

| Trial | Period of recruitment | Drugs used | Drug dose/ chemotherapy cycle | Cycles (cycles given before radiotherapy) | Radiotherapy dose (Gy)/fractions | Resection |
|---|---|---|---|---|---|---|
| EORTC 08741b (Israel *et al*[5]) | 1973-9 | Lomustine* | 70 | 13 | 45/14-25 | Complete |
| | | Cyclophosphamide | 1000 | | | |
| | | Methotrexate | 40 | | | |
| LCSG 791 (Lad *et al*[27]) | 1979-85 | Cyclophosphamide | 400 | 6 | 40/10† | Incomplete |
| | | Doxorubicin | 40 | | | |
| | | Cisplatin | 40 | | | |
| MSKCC 80-53 (Pisters *et al*[28]) | 1981-7 | Cisplatin | 120 | 4 | 46 | Complete and incomplete |
| | | Vindesine | 9 | | | |
| FLCSG3 (unpublished) | 1982-7 | Cyclophosphamide | 400 | 8 (2) | 55/20† | Incomplete |
| | | Doxorubicin | 40 | | | |
| | | Cisplatin | 40 | | | |
| GETCB 01CB82 (Chastang *et al*[29]) | 1982-6 | Doxorubicin | 40 | 3 (3) | 60-65/30-33 | Complete and incomplete |
| | | Vincristine | 1·2 | | | |
| | | Cisplatin | 75 | | | |
| | | Lomustine alternating with Cyclophosphamide | 80‡ 600 | | | |
| OLCSG 1d (Sawamura[18]) | 1983-7 | Cisplatin | 80 | 1 | 40/20 | Complete |
| | | Tegafur* | 600-800 | Daily treatment | | |
| EORTC 08861 (unpublished) | 1986-90 | Cisplatin | 100 | 4 (2) | 56/28 | Complete |
| | | Vindesine | 6 | | | |

See appendix 2 for full names of trial groups. *Given orally. †Split course of radiotherapy. ‡Total dose.

which used a combination of cisplatin and vinca alkaloids or etoposide. The intended dose of cisplatin ranged from 40 mg/m² to 120 mg/m² per cycle, with total doses of 280 mg/m² upwards, including several trials in which chemotherapy was given until the disease progressed or the toxicity was unacceptable. In this advanced disease setting, however, many patients would not have received the planned number of treatment cycles. One trial allowed entry of only patients with metastatic disease; the rest included patients with both locally advanced and advanced disease.

There was again considerable overall statistical heterogeneity ($P<0.0001$) and a pronounced difference in the results for the different chemotherapy categories ($P=0.003$) (table II, fig 7). The result for trials using long term alkylating agents suggests a detriment of chemotherapy, with a hazard ratio of 1·26. With only two such trials, however, the confidence interval was wide (0·96 to 1·66) and the result did not reach conventional levels of significance ($P=0.095$). The cisplatin based trials showed a benefit of chemotherapy, with a hazard ratio of 0·73 ($P<0.0001$), a reduction in the risk of death of 27%, equivalent to an absolute improvement in survival of 10% (5% to 15%) at one year, or an increased median survival of 1½ months (1 month to 2½ months). One

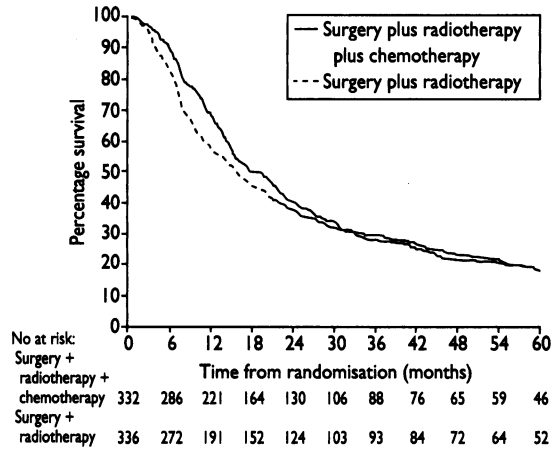


FIG 4—*Survival in trials of surgery plus radiotherapy versus surgery plus radiotherapy plus chemotherapy (only trials using regimens based on cisplatin)*

trial (CEP-85) showed an extreme result in favour of chemotherapy. Even if this trial was excluded from the analysis, however, the result was still significant in favour of chemotherapy (hazard ratio 0·77 (0·63 to 0·85), $P=0.001$). When this trial was removed, no gross statistical heterogeneity existed within the cisplatin based category ($\chi^2_{HetC}=10.91$, df=6,

| Trial | No of events/ No of patients entered: Surgery plus radiotherapy plus chemotherapy | Surgery plus radiotherapy | Observed − expected deaths | Variance |
|---|---|---|---|---|
| Long term alkylating agents: | | | | |
| EORTC 08741 | 33/66 | 40/73 | 4.87 | 16.20 |
| Subtotal | 33/66 | 40/73 | 4.87 | 16.20 |
| Cisplatin based: | | | | |
| LCSG 791 | 68/82 | 75/90 | -5.62 | 35.40 |
| MSKCC 80-53 | 32/36 | 27/36 | 3.05 | 14.51 |
| FLCSG3 | 34/40 | 42/46 | -3.20 | 18.86 |
| GETCB 01CB82 | 120/138 | 113/129 | -3.11 | 57.92 |
| OLCSG 1d | 13/26 | 10/23 | 0.12 | 5.62 |
| EORTC 08861 | 5/10 | 7/12 | 0.16 | 2.67 |
| Subtotal | 272/332 | 274/336 | -8.60 | 134.98 |
| Total | 305/398 | 314/409 | -3.73 | 151.19 |

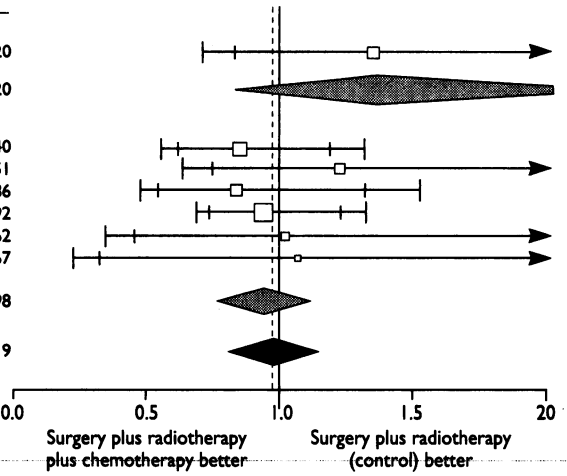


FIG 3—*Results of trials of surgery plus radiotherapy versus surgery plus radiotherapy plus chemotherapy (test for heterogeneity $\chi^2_{HeT}=3.62$, df=6, P=0·73; test for interaction $\chi^2_{HeB}=1.92$, df=1, P=0·17 (see fig 1 for explanation of plot)) (see tables for references to trials). Symbols and conventions as in figure 1*

TABLE IV—*Trials comparing radical radiotherapy with radical radiotherapy plus chemotherapy. Drugs were given intravenously and doses per cycle were in mg/m² unless stated otherwise*

| Trial | Period of recruitment | Drugs used | Drug dose/ chemotherapy cycle | Cycles (cycles given before radiotherapy | Radiotherapy dose (Gy)/fractions |
|---|---|---|---|---|---|
| NRH NSC 26271 (Host[30]) | 1968-71 | Cyclophosphamide followed by Cyclophosphamide* | 400† 100 | Daily treatment Until tumour progression or toxicity | 50/25-31 |
| EORTC 08742 (Israel *et al*[31]) | 1973-80 | Cyclophosphamide Lomustine* Methotrexate | 1000 100 40 | 12 | 50-60/Not known |
| RTOG 7302a (Simpson *et al*[32]) | 1973-8 | Cyclophosphamide | 1000 | Until tumour progression or toxicity | 40/10‡ |
| RTOG 7302b (Simpson *et al*[32]) | 1973-8 | Cyclophosphamide | 1000 | Until tumour progression or toxicity | 30/10 |
| RTOG 7302c (Simpson *et al*[32]) | 1973-8 | Cyclophosphamide | 1000 | Until tumour progression or toxicity | 40/20 |
| MCL-1 (Sidorowitz[33]) | 1980-4 | Doxorubicin Lomustine* Cyclophosphamide Methotrexate | 40 30 400 30 | Until tumour progression or toxicity or 34 | 55/25‡ |
| Aviano (Trovo *et al*[34]) | 1980-4 | Doxorubicin Cyclophosphamide Methotrexate Procarbazine* | 40 600 30 1000 | 12 | 45/15 |
| AZ-0C-1-80 (Schallier *et al*[35]) | 1981-5 | Vinblastine | 6 | Until tumour progression or toxicity | 55/28 |
| Gwent 3 (unpublished) | 1981-5 | Etoposide* | 1000 | 7 | 32/8 |
| SECSG81 LUN 373 (Johnson *et al*[36]) | 1981-5 | Vindesine followed by Vindesine | 3 6 | 5 10 | 60/33 |
| Gwent 1 (Anderson *et al*[37]) | 1974-6 | Doxorubicin Fluorouracil | 50 1200§ | 4 | 32/8 |
| SWOG 7635 (White *et al*[38]) | 1977-9 | Doxorubicin | 50 | 8 | 60/20‡ |
| NCCTG 822451 (Morton *et al*[39]) | 1983-7 | Doxorubicin Cyclophosphamide Methotrexate Lomustine* | 40 400 40 30 | 4 (2) | 60/30 |
| Buenos Aires (Cardiello *et al*[40]) | 1981-5 | Cisplatin Doxorubicin Cyclophosphamide | 40 40 400 | 6 | 55/22‡ |
| Brussels (Van Houtte *et al*[41]) | 1981-4 | Cisplatin Etoposide Vindesine | 60 360 3 | 3 (3) | 55/28 |
| FLCSG 2 (Mattson *et al*[42]) | 1982-4 | Cisplatin Doxorubicin Cyclophosphamide | 40 40 400 | 6 (3) | 55/20‡ |
| Essen (Alberti *et al*[43]) | 1983-7 | Cisplatin Vindesine | 80 6 | 3 (3) | 52-56/13-14 |
| SLCSG (Brodin *et al*[44]) | 1983-9 | Cisplatin Etoposide | 120 300 | 3 (3) | 56/28 |
| CEBI 138 (Le Chevalier *et al*[45]) | 1983-9 | Cisplatin Cyclophosphamide Vindesine Lomustine* | 100 600 3 75 | 6 (3) | 65/26 |
| WSLCRG/FI (Gregor *et al*[46]) | 1984-9 | Cisplatin Vindesine | 100 6 | 8 (2) | 50/20 |
| Perugia (Crino *et al*[47]) | 1984-8 | Cisplatin Etoposide | 100 360 | 3 (3) | 56/30 |
| CALGB 8433 (Dillman *et al*[48]) | 1984-7 | Cisplatin Vinblastine | 100 5 | 2 (2) 5 (5) | 60/30 |
| EORTC 08842 (unpublished) | 1984-9 | Cisplatin Vindesine | 100 6 | 3 (2) | 55/20‡ |
| SWOG 8300a (unpublished) | 1984-8 | Fluorouracil Vincristine Mitomycin C alternating with Cisplatin Doxorubicin Cyclophosphamide | 1200 2 10 40 40 400 | 6 (2) | 58/29 |
| SWOG 8300b (unpublished) | 1984-8 | Fluorouracil Vincristine Mitomycin C alternating with Cisplatin Doxorubicin Cyclophosphamide | 1200 2 10 40 40 400 | 6 (2) | 58/29 |

SWOG8300 also randomised to patients receiving (SWOG8300b) or not receiving (SWOG 8300a) prophylactic cranial irradiation.
See appendix 2 for full names of trial groups.
*Given orally. †Daily during radiotherapy. ‡Split course of radiotherapy. §Total dose.

P=0·09). Survival curves in this setting are drawn only to two years as few patients were alive after this time (fig 8).

### TREATMENT EFFECT IN PATIENT SUBGROUPS

Predefined subgroups of patients were analysed to determine if evidence existed of a different size of treatment effect in any such group. To minimise heterogeneity, only cisplatin based regimens were included in this analysis. Data on stage were available for 92% of patients, performance status for 94% of patients, and age, sex, and histological cell type for more than 99% of patients. No evidence existed that any group of patients specified by age, sex, histological cell type, performance status, or stage benefited more or less from chemotherapy (figure 9 shows stage, histological cell type, and performance status; more detailed plots and results for age and sex are available on request).

## Discussion

This meta-analysis was based on an extensive dataset comprising 9387 patients from 52 randomised clinical trials that compared local surgical or radiotherapy treatment or best supportive care with the same treatment plus chemotherapy in non-small cell lung cancer. Only six other eligible trials were found, for which data were not available; these were mostly older trials using chemotherapy regimens based on the long term administration of oral alkylating agents, regimens that are no longer used. For the modern, cisplatin

TABLE V—*Trials comparing supportive care with supportive care plus chemotherapy. Drugs were given intravenously and doses per cycle were in mg/m² unless stated otherwise*

| Trial | Period of recruitment | Drugs used | Drug dose/ chemotherapy cycle | Max no of cycles |
|---|---|---|---|---|
| Oxford (Laing *et al*[53]) | 1970-3 | (i) Procarbazine* | 2·5†‡ | Daily treatment 1 year |
| | | (ii) Nitrogen mustard | 0·3† | 11 |
| | | Vinblastine | 0·5† | |
| | | Procarbazine* | 35† | |
| | | Prednisolone | 560† | |
| Quebec (Cormier *et al*[54]) | 1978-9 | Methotrexate | 40 | Until tumour progression or toxicity |
| | | Doxorubicin | 40§ | |
| | | Cyclophosphamide | 400 | |
| | | Lomustine* | 30 | |
| Gwent 2 (Anderson *et al*[55]) | 1982-4 | Etoposide* | 600 | 6 |
| RLW 8351 (Woods *et al*[56]) | 1982-6 | Cisplatin | 120 | Until tumour progression or toxicity |
| | | Vindesine | 3 | |
| NCIC CTG BR5 (Rapp *et al*[57]) | 1983-6 | (i) Cisplatin | 120 | Until tumour progression or toxicity |
| | | Vindesine | 3 | |
| | | (ii) Cisplatin | 40 | Until tumour progression or toxicity |
| | | Doxorubicin | 40 | |
| | | Cyclophosphamide | 400 | |
| Southampton (Woods *et al*[58]) | 1983-6 | Cisplatin | 120 | 6 |
| | | Vindesine | 3 | 15 |
| NRH (Kaasa *et al*[59]) | 1983-7 | Cisplatin | 70 | 4 |
| | | Etoposide | 100 | |
| | | Etoposide* | 400 | |
| UCLA (Ganz *et al*[59]) | 1984-6 | Cisplatin | 120 | Until tumour progression or toxicity |
| | | Vinblastine | 6 | Until tumour progression or toxicity |
| Ancona 1 (Cellerino *et al*[60]) | 1985-8 | Cisplatin | 80 | Until tumour progression or toxicity |
| | | Cyclophosphamide | 500 | |
| | | Epirubicin alternating with | 50 | |
| | | Methotrexate | 30 | |
| | | Etoposide | 200 | |
| | | Lomustine* | 70 | |
| AOI-Udine (Cartei *et al*[61]) | 1984-6 | Cisplatin | 75 | 6 |
| | | Cyclophosphamide | 400 | |
| | | Mitomycin C | 10 | |
| CEP-85 (Quoix *et al*[62]) | 1985-8 | Cisplatin | 120 | 8 |
| | | Vindesine | 3 | 18 |

See appendix 2 for full names of trial groups. Roman numerals indicate multiple treatment arms.
*Given orally.
†Dose in mg/kg.
‡Dose escalating to 5 mg/kg during weeks 3-6 then reduced to starting dose.
§Stopped at total dose 450 mg/m².

based regimens data from approximately 95% of all patients ever entered into all known relevant trials were analysed. Furthermore, for almost all trials the data on individual patients had been updated to the point of data collection, which was often many years after the publication of the trial's results. This meta-analysis therefore provides the most comprehensive and reliable current assessment of the average treatment effect of broad categories of chemotherapy regimens among broad classes of patients with non-small cell lung cancer.

One of the most striking aspects of the results is the consistency in the direction, and indeed in the estimated hazard ratios, of the various chemotherapy categories among the different primary treatments compared (table II). This consistency allows stronger conclusions to be drawn than perhaps could be inferred from each of the individual results.

In the early and advanced disease settings older trials using long term alkylating agents tended to show a detrimental effect of chemotherapy. This effect was conventionally significant for the adjuvant surgical trials. Chemotherapies of the type used in the early 1970s based on long term administration of alkylating agents are therefore likely to be detrimental to patients with non-small cell lung cancer. The mechanism for this is unknown, although some occurrences of leukaemia after treatment with busulphan have been described for non-small cell lung cancer,[64] and a possible model for an observed detrimental effect of cyclophosphamide and other alkylating agents in non-small cell lung cancer has been proposed.[65] Clearly, such regimens are not used today, but the result may have implications for other disease sites, although the

| Trial | No of events/ No of patients entered: Radiotherapy plus chemotherapy | Radiotherapy | Observed − expected deaths | Variance |
|---|---|---|---|---|
| Long term alkylating agents: | | | | |
| NRH NSC-26271 | 36/36 | 38/38 | -1.63 | 17.55 |
| EORTC 08742 | 45/53 | 51/64 | -1.91 | 23.36 |
| RTOG 7302a | 52/55 | 48/56 | 4.58 | 23.23 |
| RTOG7302b | 38/46 | 43/50 | 0.84 | 19.31 |
| RTOG7302c | 38/47 | 53/57 | -3.08 | 22.19 |
| MCL-1 | 16/25 | 19/27 | -2.79 | 8.49 |
| Aviano | 47/49 | 61/62 | 1.15 | 26.09 |
| Subtotal | 272/311 | 313/354 | -2.83 | 140.23 |
| Vinca alkaloids/etoposide: | | | | |
| AZ-OC-1-80 | 22/27 | 23/25 | -4.56 | 10.35 |
| Gwent 3 | 40/41 | 43/44 | -0.06 | 20.25 |
| SECSG 81 LUN375 | 94/107 | 97/105 | -5.94 | 47.21 |
| Subtotal | 156/175 | 163/174 | -10.55 | 77.80 |
| Other drugs: | | | | |
| Gwent 1 | 23/26 | 30/30 | -6.11 | 12.47 |
| SWOG 7635 | 25/30 | 23/32 | 6.04 | 10.44 |
| NCCTG 822451 | 54/58 | 59/63 | -1.03 | 28.04 |
| Subtotal | 102/114 | 112/125 | -1.10 | 50.95 |
| Cisplatin based: | | | | |
| Buenos Aires | 43/43 | 35/38 | -3.57 | 18.26 |
| Brussels | 25/31 | 29/34 | 4.18 | 12.31 |
| FLCSG 2 | 124/125 | 126/127 | -2.49 | 62.14 |
| Essen | 21/22 | 22/26 | 2.09 | 9.80 |
| SLCSG | 159/163 | 161/164 | -12.39 | 77.92 |
| CEBI 138 | 166/176 | 173/177 | -21.95 | 82.68 |
| WSLCRG/FI | 37/40 | 35/39 | -1.61 | 17.82 |
| Perugia | 32/33 | 32/33 | -4.45 | 14.84 |
| CALGB 8433 | 73/89 | 80/91 | -13.39 | 37.13 |
| EORTC 08842 | 36/38 | 37/37 | -3.23 | 17.70 |
| SWOG 8300a | 62/64 | 62/64 | -3.07 | 30.19 |
| SWOG 8300b | 63/63 | 63/63 | 2.81 | 30.38 |
| Subtotal | 841/887 | 855/893 | -57.08 | 411.18 |
| Total | 1371/1487 | 1443/1546 | -71.56 | 680.16 |

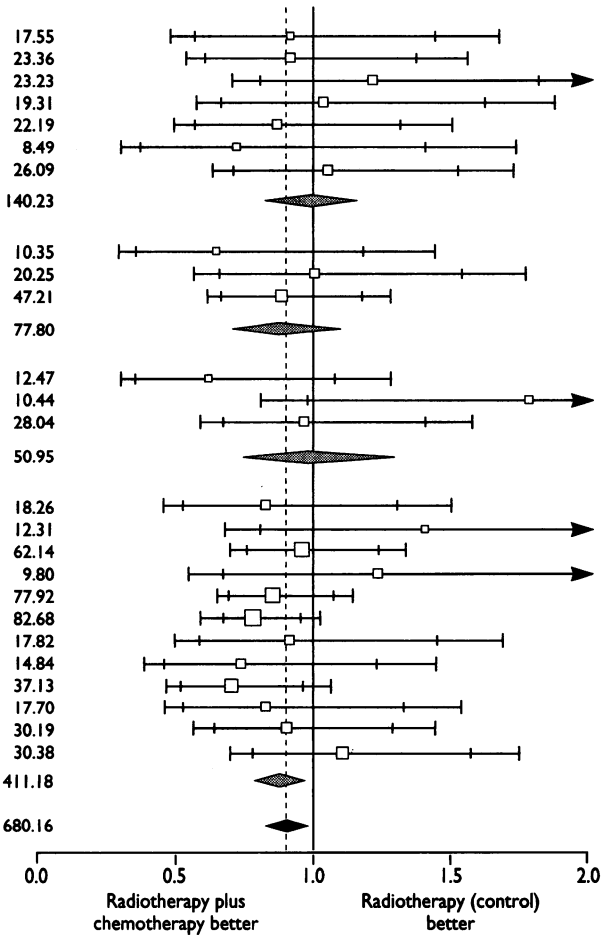


FIG 5—*Results of trials of radical radiotherapy versus radical radiotherapy plus chemotherapy (test for heterogeneity $\chi^2_{HetT}=22{\cdot}33$, $df=24$, $P=0{\cdot}560$; test for interaction $\chi^2_{HetB}=1{\cdot}91$, $df=3$, $P=0{\cdot}592$ (see fig 1 for explanation of plot)) (see tables for references to trials). Symbols and conventions as in figure 1*

administration of chemotherapy and the drugs used have changed a lot over the past 20 years.

In all comparisons, results for modern regimens containing cisplatin favoured chemotherapy. These were conventionally significant in the locally advanced and supportive care settings. However, we emphasise that the categorisation of drug regimens was chosen mainly as an objective way of classifying modern chemotherapy. Furthermore, several cisplatin based regimens were used, and it is not possible to deduce to what extent the observed effects were due to the cisplatin or to the other drugs, in the combinations studied. Indeed cisplatin was used in combination with vinca alkaloids or etoposide in two thirds of trials. It is therefore not possible to recommend a particular regimen over another. Further randomised trials are needed to determine which regimens are the most effective of the modern chemotherapies studied.

Trials using regimens containing vinca alkaloids or etoposide and those in the "other drugs" category also always tended to favour chemotherapy, although for these categories the confidence intervals were relatively wide and no reliable conclusions can be drawn. The meta-analysis provided no evidence that modern, cisplatin based chemotherapy was more or less effective in any particular subgroup of patients. Thus no good evidence exists that the relative effect of chemotherapy is any smaller or larger for any particular type of patient. Nevertheless, as certain types of patient may have intrinsically different prognoses and consequently differing baseline survivals, the same relative effect may provide different absolute differences in survival. For example, the hazard ratio of 0·87 for adjuvant chemotherapy would increase the survival of patients with a good prognosis from a baseline of, say, 80%, to 82% but patients with a poor prognosis from a baseline of, say, 40%, to 45% at two years. Similarly, the same observed hazard ratio of 0·87 in the locally advanced setting would increase the survival of patients with a good prognosis from a baseline of, say, 30%, to 35% and patients with a poor prognosis from 5% to 7%.

The meta-analysis suggests that modern chemotherapy regimens may provide absolute benefits of about 5% in the surgical and 2% in the radical radiotherapy setting at five years and 10% at one year in the supportive care setting. The confidence intervals are such, however, that the results are consistent with benefits of as much as 10%, 4%, and 15% respectively or with as little as a 1% detriment and 1% and 5% benefits respectively. Although modest, such improvements can, given the high incidence of lung cancer, be important in public health terms, and studies of patients' opinions of treatments for cancer have shown that many patients accept considerable toxicity in return for small improvements in survival.[66] However, patients are not uniform in their preferences, and the trade offs involved in choosing between more and less

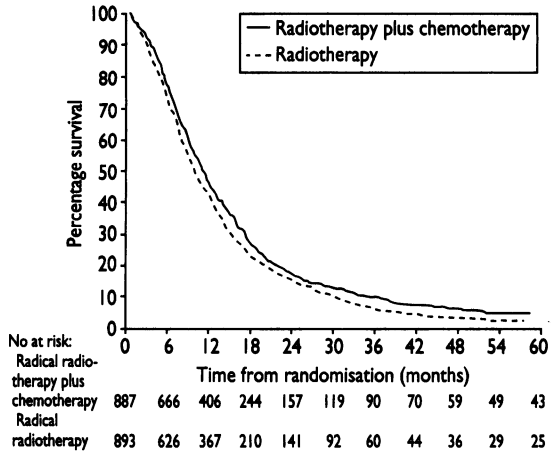


FIG 6—*Survival in trials of radical radiotherapy versus radical radiotherapy plus chemotherapy (only trials using regimens based on cisplatin)*

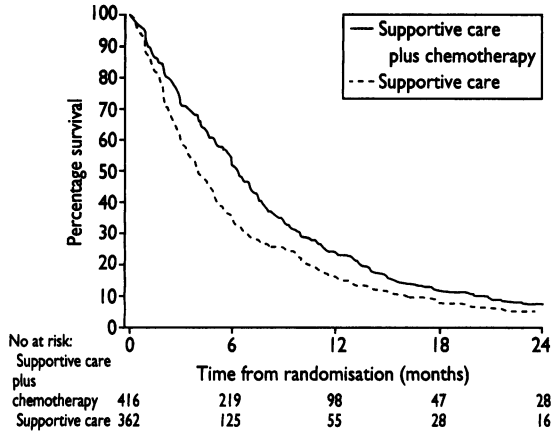


FIG 8—*Survival in trials of supportive care versus supportive care plus chemotherapy (only trials using regimens based on cisplatin)*

| Trial | No of events/No of patients entered: Supportive care plus chemotherapy | Supportive care | Observed − expected deaths | Variance |
|---|---|---|---|---|
| Long term alkylating agents: | | | | |
| Oxford | 120/121 | 62/67 | 16.40 | 43.80 |
| Quebec | 20/20 | 18/18 | -4.38 | 7.99 |
| Subtotal | 140/141 | 80/85 | 12.02 | 51.79 |
| Vinca alkaloids/etoposide: | | | | |
| Gwent 2 | 96/111 | 67/75 | -5.15 | 38.00 |
| Subtotal | 96/111 | 67/75 | -5.15 | 38.00 |
| Cisplatin based: | | | | |
| RLW 8351 | 84/86 | 80/81 | -8.06 | 39.94 |
| NCIC CTG | 95/97 | 51/53 | -11.28 | 28.24 |
| Southampton | 17/17 | 15/15 | 1.16 | 7.55 |
| NRH | 44/44 | 40/43 | 2.93 | 18.72 |
| UCLA | 31/32 | 30/31 | -4.83 | 14.53 |
| Ancona I | 63/63 | 65/65 | -5.72 | 30.95 |
| AOI-Udine | 52/52 | 50/50 | -14.98 | 18.77 |
| CEP-85 | 23/25 | 21/24 | -10.52 | 6.61 |
| Subtotal | 409/416 | 352/362 | -51.31 | 165.31 |
| Total | 645/668 | 499/522 | -44.44 | 255.09 |

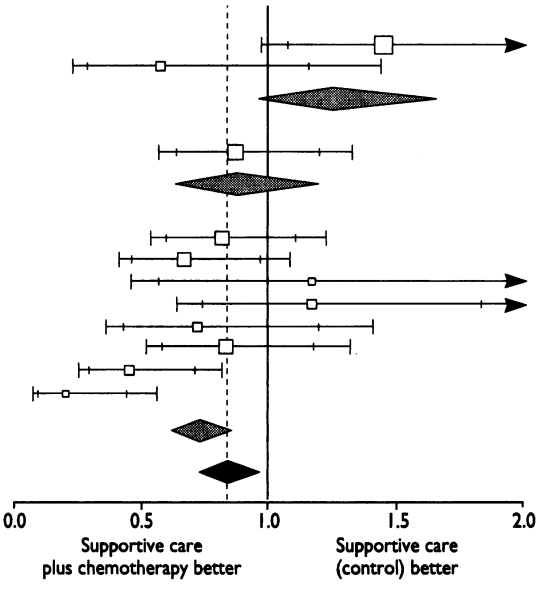


FIG 7—*Results of trials of supportive care versus supportive care plus chemotherapy (test for heterogeneity $\chi^2_{HeT}=39{\cdot}65$, $df=10$, $P=<0{\cdot}0001$; test for interaction $\chi^2_{HeB}=11{\cdot}67$, $df=2$, $P=0{\cdot}003$ (see fig 1 for explanation of plot)) (see tables for references to trials). Symbols and conventions as in figure 1*

intensive therapy are not necessarily straightforward and warrant further study.[67]

IMPLICATIONS FOR RESEARCH

Extended follow up on existing trials and the inclusion of current randomised trials will add to the evidence of subsequent updates of this meta-analysis. Nevertheless, further randomised trials are still needed, especially in early disease. Moderately sized developmental trials, recruiting a few hundred patients, are needed to screen new treatment regimens and new methods of delivering treatments, thus attempting to improve long term survival. Large public health trials, recruiting thousands of patients, are also needed to assess the value of short term chemotherapies in a broad range of patients with non-small cell lung cancer. Such trials have already been launched in Europe as a consequence of this meta-analysis.

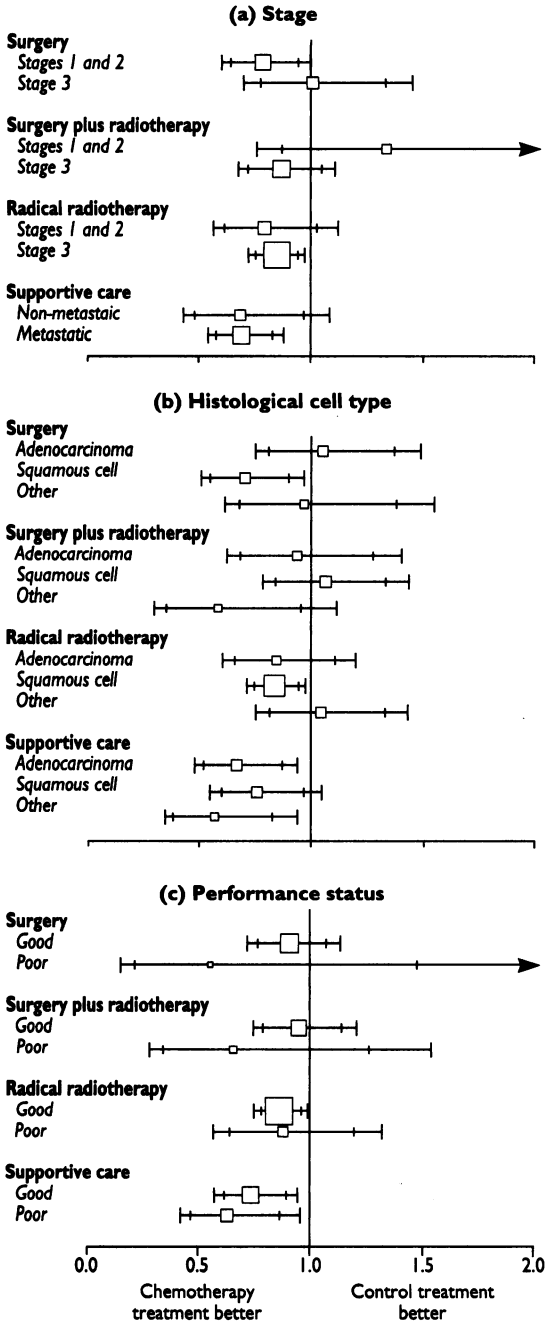


FIG 9—*Treatment effect (test for interaction) in cisplatin based trials according to (a) stage: surgery* $\chi^2_{HetB}=2{\cdot}33$, $P=0{\cdot}13$; *surgery plus radiotherapy* $\chi^2_{HetB}=3{\cdot}30$, $P=0{\cdot}07$; *radical radiotherapy* $\chi^2_{HetB}=0{\cdot}15$, $P=0{\cdot}70$; *supportive care* $\chi^2_{HetB}=0{\cdot}01$, $P=0{\cdot}92$; *(b) histological evidence: surgery* $\chi^2_{HetB}=5{\cdot}4$, $df=2$, $P=0{\cdot}07$; *surgery plus radiotherapy* $\chi^2_{HetB}=4{\cdot}71$, $df=2$, $P=0{\cdot}09$; *radical radiotherapy* $\chi^2_{HetB}=2{\cdot}59$, $df=2$, $P=0{\cdot}27$; *supportive care* $\chi^2_{HetB}=1{\cdot}66$, $df=2$, $P=0{\cdot}44$; *and (c) performance status: surgery* $\chi^2_{HetB}=0{\cdot}96$, $P=0{\cdot}33$; *surgery plus radiotherapy* $\chi^2_{HetB}=1{\cdot}13$, $P=0{\cdot}29$; *radical radiotherapy* $\chi^2_{HetB}=0{\cdot}01$, $P=0{\cdot}92$; *supportive care* $\chi^2_{HetB}=0{\cdot}66$, $P=0{\cdot}42$. *Symbols and conventions as in figure 1. The various conventional staging and scoring systems used in the trials were converted to common meta-analysis categories (details of these conversions are available on request)*

**Key messages**

- It has been unclear whether chemotherapy has a role in treating non-small cell lung cancer despite over 30 years of research
- This international collaborative meta-analysis collected updated data on individual patients from 9387 patients included in 52 randomised clinical trials
- This meta-analysis provides the currently most reliable estimates of the average effect of chemotherapy in broad classes of non-small cell lung cancer
- Modern chemotherapy regimens may have a role in treating all stages of non-small cell lung cancer, although further research is needed to confirm the suggestion of benefit
- Further clinical trials are needed to assess short term chemotherapy and to compare different chemotherapies

IMPLICATIONS FOR PRACTICE

Although, inevitably, meta-analyses give only average estimates of treatment effects, these are probably the best estimates on which to base treatment policy. At the outset of this meta-analysis there was considerable pessimism about the treatment of non-small cell lung cancer. Although the observed effects are modest, these results offer hope of progress and show that chemotherapy may have a role in treating this disease. Some patients and clinicians would need to observe larger treatment effects than others before being convinced that chemotherapy is worth while, and undoubtedly these results will be applied differently by individual clinicians and patients around the world. Some groups may consider these results to be good enough evidence to use cisplatin based chemotherapy for certain patients. As essential drugs were not determined by this meta-analysis, however, others may need further evidence to decide whether to use chemotherapy routinely in the treatment of non-small cell lung cancer.

Just as no clinical trial can provide "prescriptions" of how to treat individual cases, neither can a meta-analysis. Ultimately, the use of chemotherapy is to be decided by the clinician and patient together and will depend on many factors, including survival, toxicity, quality of life, and economic cost of treatment. This meta-analysis provides clinicians and patients with the current most reliable estimate of average survival benefit to use as part of this decision making process.

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## Appendix 1

*Ineligible trials*—Four trials were not properly randomised, including one randomised by date of birth and two using historical controls. Three trials allowed prior chemotherapy and seven used compounds that were not considered to be established chemotherapy (mopidamol, razoxane, lonidamine, RSV (1,2-diphenyl-αβ-dicetone and its superoxide), sizofiran). One early trial randomised all lung cancers but did not record histological cell type. Four trials were confounded because they used different radiotherapy doses or schedules per arm. Fourteen trials used chemotherapy only during radiotherapy or stated chemotherapy was given with the aim of radiosensitisation, or did both, including three that were also ineligible for other reasons. A full list of these trials is available on request.

*Unavailable trials*—Six trials were not available for analysis; two were early trials in the surgical setting,[25 26] and four were from the locally advanced setting,[49-52] only one of which was a modern trial using cisplatin based chemotherapy.[52]

## Appendix 2

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|---|---|
| AOI-Udine | Udine Associazione Oncologica Italiana |
| AZ-OC | Academisch Ziekenhuis Oncologic Centre (Vrije Universiteit Brussels) |
| Buenos Aires | Hospital Militar Central, Buenos Aires |
| CALGB | Cancer and Leukemia Group B |
| CEP | Cercle d'Etudes Pneumologiques (Strasbourg) |
| EORTC | European Organisation for Research and Treatment of Cancer |
| FI | Finsen Institute, Copenhagen |
| FLCSG | Finnish Lung Cancer Study Group |
| GETCB | Groupe d'Etude et de Traitement des Cancers Bronchiques |
| IPCR, Chiba | Institute of Pulmonary Cancer Research, Chiba, Japan |
| JLCSSG | Japan Lung Cancer Surgical Study Group |
| LCSG | Lung Cancer Study Group |
| MCL | McGill Cancer Center, Lung |
| MRC | British Medical Research Council |
| MSKCC | Memorial Sloan Kettering Cancer Center |
| NCCTG | North Central Cancer Treatment Group |
| NCI | National Cancer Institute |
| NCIC CTG | National Cancer Institute of Canada, Clinical Trials Group |
| NRH | Norwegian Radium Hospital |
| OLCSG | Osaka Lung Cancer Study Group |
| RLW | Royal North Shore Hospital, St Leonards, NSW |
| RTOG | Radiation Therapy Oncology Group |
| SCG | Swiss Chemotherapy Group |
| SECSG | Southeastern Cancer Study Group |
| SGACLC | Study Group of Adjuvant Chemotherapy for Lung Cancer, Chibu, Japan |
| SLCSG | Swedish Lung Cancer Study Group |
| SWOG | South West Oncology Group |
| UCLA | University of California at Los Angeles (Solid Tumour Study Group) |
| VASAG | Veterans Administration Surgical Adjuvant Group |
| VASOG | Veterans Administration Surgical Oncology Group |
| WJSG | West Japan Study Group for Lung Cancer Surgery |
| WPL | Working Party for Lung Cancer (Committee on Surgery and Surgery Consultants) |
| WSLCRG | West of Scotland Lung Cancer Research Group |

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## ONE HUNDRED YEARS AGO

### THE COST OF A MEDICAL EDUCATION.

There are few things more serious than the choice of a profession, and there is no doubt that in many homes at the present time anxious family councils are being held regarding the career of lads who are now leaving school, and must in some way or another be launched upon the world. Among the careers in which the highest prizes are open to all who have wit and energy and can afford the cost of the necessary course of study, medicine offers to many the highest attractions. The scientific character of the study, the purely personal nature of the work, the life of intimacy with many people of many ranks, the possibility —dim perhaps, but still the possibility—of wealth and honour, and the almost certainty at least of bread and cheese as the reward of patience, sobriety, and hard work, are sure to draw many to medicine as their career in life. It would be well, however, before coming to a decision, that they should consider the drawbacks and the hardships. No one will deny that the prizes are great and that those who win them find their way smoothed to wealth, influence, and position. These, however, are but few. It must not be thought that all men of consulting rank, however successful they may be in science, are successful also as the world counts success. No; to the immense majority who next October commence their professional studies medicine will prove but a harsh mother, and will give little beyond the necessaries of a simple and frugal life. (*BMJ* 1895;ii:574.)